Preoperative Cardiac Function Parameters as Valuable Predictors for Nurses to Recognize Delirium after Cardiac Surgery: a prospective cohort study

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IMPLICATIONS FOR PRACTICE

- We suggest incorporating an early determination of the preoperative cardiac function as a readily available risk assessment for delirium warning prior to cardiac surgery.
- Nurses should pay more attention and preventive measures should be applied to patients with poor preoperative cardiac function to reduce the incidence of delirium after cardiac surgery.
- Future research is needed to generate a greater understanding of the pathophysiological association between heart dysfunction and delirium following cardiac surgery.

Abstract

Background: Delirium is a common postoperative complication after cardiac surgery. The relationship between delirium and cardiac function has not been fully elucidated.

Aims: The aim of this study is to identify the association between preoperative cardiac function and delirium among patients after cardiac surgery.

Methods: We prospectively recruited 635 cardiac surgery patients with a planned cardiac intensive care unit (ICU) admission. Postoperative delirium was diagnosed using Confusion Assessment Method for ICU. Preoperative cardiac function was assessed using N-Terminal prohormone of Brain Natriuretic Peptide (NT-proBNP), New York Heart Association (NYHA) functional classification and Left Ventricular Ejection Fraction (LVEF).

Results: Delirium developed in 73 patients (11.5%) during ICU stay. NT-proBNP level (odds ratio (OR) 1.24 (95%CI, 1.01-1.52)) and New York Heart Association (NYHA) functional classification (OR 2.34 (95%CI, 1.27-4.31)) were both independently associated with the occurrence of delirium after adjusting for various confounders. The OR of delirium increased with increasing NT-proBNP levels after the turning point of 7.8 (log-transformed pg/ml). The adjusted regression coefficients were 1.19 (95% CI: 0.95-1.49, p=0.134) for NT-proBNP < 7.8 (log-transformed pg/ml) and 2.78 (95% CI: 1.09-7.12, p=0.033) for NT-proBNP >7.8 (log-transformed pg/ml). No association was found between LVEF and post-operative delirium.

Conclusion: Preoperative cardiac function parameters including NT-proBNP and NYHA functional classification can predict the incidence of delirium following

cardiac surgery. We suggest incorporating an early determination of preoperative cardiac function as a readily available risk assessment for delirium prior to cardiac surgery.

The study was registered with the US National Institutes of Health ClinicalTrials.gov (NCT03704324).

Keywords: Cardiac surgery, Cardiac function, Delirium, Predictors, Intensive Care Units.

INTRODUCTION

Delirium is an acute and fluctuating alteration of mental state characterized by disturbances in attention, consciousness and cognition[1]. Postoperative delirium (POD) is a common postoperative complication that can appear in patients of any age[2]. A meta-analysis reported that the estimated prevalence of delirium after cardiac surgery ranges from 2% to 73%[3]. The reported incidence of POD varies within a broad range of different patients due to different risk factors exposure[4]. POD is associated with several negative outcomes, including more mechanically ventilated days, increased hospital length-of-stay (LOS) and higher cost which impose substantial burdens on patients and their families[5]. Additionally, delirium brings great burden to patients and their families as the follow-up cognitive decline can last for months to years hindering patients to return to their previous quality of life and employment[6]. Therefore, intensive care nurses are at the forefront in preventing delirium in intensive care patients. The mechanisms of delirium are still uncovered and effective treatment is lacking at present[7]. Particular for nursing practice it is important to identify risk factors of delirium to early detect and prevent the development of delirium[8].

Although the number of studies on delirium has increased in the past decade, an evidence gap still exists in this area due to the heterogeneity of previous studies and their results. Thus far, age, cerebrovascular diseases and cognitive functions are the only three identified factors with strong evidence[9]. However, only a few studies have focused on the relationship between delirium and cardiac function. Cardiac dysfunction, even heart failure, commonly exists among patients before cardiac surgery. However, the relationship between preoperative heart function and postoperative delirium has not been fully elucidated[10]. The three parameters of preoperative cardiac function included in this study were N-Terminal prohormone of Brain Natriuretic Peptide (NT-proBNP), the New York Heart Association (NYHA) functional classification and the Left Ventricular Ejection Fraction (LVEF). These three parameters are clinical available and commonly used in our department and hospital. Additionally, these three parameters can reflect the cardiac function in multi-dimensional way. We hypothesized that preoperative cardiac function of patients might be associated with postoperative delirium, and which could be valuable predictors for delirium after cardiac surgery. Therefore, the objective of this study is to identify the association between three parameters of preoperative cardiac function and delirium among patients after cardiac surgery.

METHODS

Design

This is a single-centre, prospective cohort study conducted at a tertiary teaching hospital in Shanghai, China. There were two reasons that we chose prospective cohort study: 1. The prospective study design allowed us to select the expected variables and design the collection plan ahead. The data was more complete and precise than retrospective study. 2. The primary outcome was the development of postoperative delirium which needed professional assessment and diagnosis. The follow-up delirium assessment in prospective cohort study could improve the assessment quality and reliability which could reduce the measurement bias. Furthermore, this study is part of a larger study to develop a delirium prediction model for all surgical intensive care patients[11].

The study has been reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement[12].

Participants

We calculated the sample size based on the incidence of postoperative delirium. The reported incidence was ranged from 3.6% to 53.3%[8]. We used the lowest incidence 3.6% to estimate the sample size of 253 with a precision of 5% and confidence level of 95%[13, 14]. On the other hand, we calculated the sample size based on the rule of thumb in logistic modelling: a minimum of 20 events per predictor variable (EPV) should be achieved based on simulation studies[15]. The expected variable number included in logistic model was twenty and in consideration of 15% of loss to follow-up, the sample size was 460. Furthermore, we estimated the number of admissions of the cardiac department in our institute, which could offer sufficient sample size to this study.

Participants were prospectively consecutively recruited from November 1 2018 to January 31 2019. We included patients aged older than 18 years with planned admissions to the surgical ICU after the cardiac surgical procedure. We excluded patients with preoperative delirium and dementia and patients who were unable to fully participate in the delirium testing, including patients who were blind, deaf, illiterate or unable to understand Chinese. We also excluded patients who were in a coma or with deep sedation in the first five days postoperatively. Consequently, 708 patients were eligible for inclusion in this study, and 73 patients were excluded because they were lost to follow-up with regard to the delirium assessment. Finally, 635 patients were included in the analysis (Figure S1).

Setting

The study was conducted in the cardiac surgery department and cardiac surgical ICU in Zhongshan hospital, Shanghai, China, which is the largest cardiac surgery department in eastern China. In 2018, the department performed nearly 5,000 cardiac surgeries. The cardiac surgical ICU has 39 beds and the ICU staff include 121 nurses and physicians. This ICU admits around 100 postoperative patients per week.

Data Collection

Preoperative assessment

The three preoperative heart function parameters, namely, the NYHA functional classification, LVEF and NT-proBNP level, were prospectively collected. NYHA functional classification was assessed by a cardiac surgeon, the LVEF was obtained from preoperative transthoracic echocardiography, and the NT-proBNP level was measured by a laboratory tests one to three days before surgery. All enrolled patients received preoperative assessments by trained nurses. The baseline demographic data and medical history were recorded. We defined smoking or drinking habits (including prior) before surgery as nicotine use or alcohol use. The Modified Barthel Index was used to measure the activities of daily living[16]. The Hospital Anxiety and Depression Scale (HADS) was used to evaluate preoperative anxiety and depression levels. Patients were considered preoperatively anxious or depressed status when the HADS subscale scored $\geq$ 11[17]. Sleep quality was assessed as good, average or poor according to patients' self-reports, while the degrees of visual and hearing impairment were also reported by patients. We used Numerical Rating Score (NRS; scores 0-10) to evaluate the pain level of patients before surgery.

Surgery and postoperative management

A standard general anaesthesia technique was used for all patients. Different cardiac operations were performed according to the preoperative conditions of each patient. Surgical types included CABG (Coronary Artery Bypass Grafting) in 106 (16.69%) patients, valve surgery (only open heart) in 391 (61.57%) patients, aortic surgery in 91 (14.33%) patients and congenital heart disease (CHD) in 71 (11.8%) patients. After surgery, all patients were transferred to the cardiac surgical ICU and received mechanical ventilation support. Until extubation, patients were sedated with propofol and dexmedetomidine through continuous intravenous infusion to achieve targeted Richmond Agitation-Sedation Scale (RASS) scores of 0 to -3.

Outcomes

The primary outcome was the presence of POD in the ICU, which often occurs up to five days after surgery[18, 19]. Thus, each patient in our study was assessed for delirium on postoperative day 1 and the assessments continued for five days or until the patient was discharged from the ICU. When patients had sudden changes in mental status or behaviours, more frequent screening was conducted. Before the delirium assessment, the RASS[20] was used to initially estimate the mental state of patients. If patients scored -4 or -5 on the RASS, which meant they could not respond to a voice, the patients were not screened for delirium until they regained consciousness. We defined POD as at least one positive screening during the ICU stay.

The Confusion Assessment Method for ICU (CAM-ICU)[21] was commonly used to detect delirium. The CAM-ICU is a validated and reliable tool for screening for delirium and takes 2-5 min complete[22, 23]. The criteria of CAM-ICU included four features: (1) acute onset or fluctuations of mental status in past 24 hours, (2) inattention, (3) altered level of consciousness, and (4) disorganized thinking. Delirium was considered present if feature (1) and (2) plus either feature (3) or (4) existed. The Chinese versions of the screening and assessment tools have been translated and published in the latest Chinese guidelines of Chinese Medical Association Critical Care Medicine (CMACCM) Branch[24].

The assessors used the following delirium assessment technique. First, two assessors interviewed medical staff caring for the patients and reviewed the patients' medical records from the past 24 hours. After this, the assessors used the RASS and CAM-ICU to assess the status of patients. If the two assessors disagreed with the assessment results, a consensus panel consisting of two ICU physicians and one psychiatrist made the final decision. To assess the quality of the delirium assessments, inter-rater reliability measurements for the CAM-ICU were performed by generating duplicate measurements of the CAM-ICU at one week before the study. We compared the CAM-ICU scores assessed by the two assessors with the scores assessed by a CAM-ICU expert. The CAM-ICU experts and two assessors were blinded to each other's delirium assessments. The CAM-ICU screening Cohen's kappa was above 0.85 and was considered reliable.

Blinding

In order to avoid misalignment bias, the assessors in the ICU were unaware of the baseline status of the participants. The data was managed in the Research Electronic Data Capture (REDCap), which was securely locked and password-protected. It is supported and maintained by the Evidence-based centre of Fudan University. Data management and analysis were done by the biostatisticians in the centre. Each patient was given a study identification number, and paper files were imported to the database once completed.

Statistical Analysis

Data are presented as mean and standard deviation for continuous variables and as percentages for categorical variables. We log transformed the NT-proBNP level because it had a right-skewed distribution. Normally distributed continuous variables were compared using 1-way ANOVA. The Pearson χ^2 test was applied to all categorical variables. Logistic-regression models were used to investigate the effects of preoperative heart function (including NT-proBNP level, NYHA functional classification and LVEF) and the other variables on the occurrence of delirium after cardiac surgery in both univariate and multivariate analyses. Independent variables were selected based on evidence in previous studies showing a significant relation to delirium[8, 9, 25], and we also included other variables based on our clinical experience. Multiple imputation with chain equations was used for missing values. Five imputation data sets were created, including the model variables in the imputation process.

To compare the predictive values of different heart function parameters with regard to the outcome, NT-proBNP level, NYHA functional classification and LVEF were first individually entered into model 1 and then individually entered into model 2. Model 1 was adjusted for age, sex, cerebrovascular disease, duration of surgery, and intraoperative blood transfusion. Model 2 was adjusted for age, sex, cerebrovascular disease, duration of surgery, intraoperative blood transfusion, peripheral vascular disease, hypertension, diabetes mellitus, hyperlipidaemia, preoperative anxiety, preoperative depression, ADL, and blood urea nitrogen (BUN).

Restricted cubic spline was employed to estimate the dose-response relation of the log NT-proBNP level and the risk of delirium[26]. All significance tests were two-sided and $P<0.05$ was considered statistically significant. The analyses were performed using SPSS version 22.0 (IBM, New York, NY) and R statistical software (R, version 3.5.1; R Project).

Ethics

The study was registered with the US National Institutes of Health ClinicalTrials.gov (NCT03704324). The study was approved by the Zhongshan Hospital Ethics Board (B2018-071). The study was conducted in accordance with the International Council for Harmonization and Good Clinical Practice principles. All patients received written and verbal information about the study before undergoing surgery. Written informed consent forms was obtained from all patients before surgery. All the data were collected from patients interview or electronic medical system only after the written informed consent were obtained. The patients had the right to withdraw from the study at any time. Data collection was stopped, and patient records were deleted from the database if a patient withdrew from the study.

RESULTS

Patient characteristics

The primary outcome POD was not available for 73 of the 708 participants of which 26 patients were excluded due to coma or deep sedation (Figure S1). In order to demonstrated that we do not have a choice bias, we compared the group with missing primary outcomes (n=73) and the group included in the final analysis (n=635). There were no significant differences of baseline characteristics between participants with primary outcome available and those not (Table S1).

The baseline characteristics of all participants are presented in Table 1, both overall and stratified according to the four grades of NYHA functional classifications. The incidence of delirium after cardiac surgery was 11.5%. The incidence of delirium was significantly different between patients with different NYHA functional classifications.

Preoperative cardiac function and delirium

Table 2 presents the results of multivariate regression for the effects of the preoperative level of NT-proBNP, NYHA functional classification and LVEF on the incidence of POD after cardiac surgery. The three cardiac function parameters were all significantly associated with delirium in the crude model. However, only the NT-proBNP level and NYHA functional classification remained statistically significant after adjusting for strongly related factors with ORs (95% confidence interval [CI]) of 1.32 (1.09-1.60) for NT-proBNP and 2.46 (1.35-4.49) for NYHA functional classification. Additionally, even after adjusting for 13 related factors in model 2, the NT-proBNP level (OR 1.24 (95%CI, 1.01-1.52)) and NYHA functional classification (OR 2.34 (95%CI, 1.27-4.31)) were still significantly associated with the occurrence of delirium.

Non-linear relationship between NT-proBNP level and delirium

Furthermore, a non-linear relationship was observed between the NT-proBNP level and the OR for delirium. The OR for delirium increased with increasing NT-proBNP levels after the turning point of 7.8 (log transformed pg/ml). The threshold effect of the NT-proBNP level on delirium was significant after adjusting for potential confounders. The adjusted regression coefficient was 1.19 (95% CI: 0.95-1.49, p=0.134) for NT-proBNP < 7.8 (log-transformed pg/ml), while it was 2.78 (95% CI: 1.09-7.12, p=0.033) for NT-proBNP >7.8 (log-transformed pg/ml) (Figure 1).

Subgroup analysis according to NYHA functional classification

The subgroup analysis is presented in Figure 2. We found that in patients without diabetes mellitus, the NYHA functional classification had stronger effects on predicting POD, with an OR (95%CI) of 2.91 (1.63-5.18), p for interaction=0.045. No significant heterogeneity was found among other analyzed subgroups stratified according to age, gender, nicotine use, alcohol use, hypertension, history of surgery, preoperative depression, ADL and preoperative sleep quality.

DISCUSSION

Although several studies have focused on exploring factors and predictors to support early prevent of POD, an evidence gap remains that needs to be further explored. The main findings of our study were as follows: the preoperative level of NT-proBNP and NYHA functional classification can be strong predictors of POD, and the NT-proBNP level had a non-linear relationship with the incidence of delirium. Which means, the higher NT-proBNP level or NYHA functional classification might predict the higher risk to present delirium after cardiac surgery.

Existing studies are commonly characterized by several limitations, particularly wide varieties of target populations and surgical types and small sample sizes[7, 25]. Remarkably, previous studies have only explored the associations of several risk factors with POD, while the specific underlying relationships remain unclear. Moreover, few studies have focused on the relationship between preoperative heart function and POD. Consistent with our study, Uthamalingam et al. found that 17.1% of patients with acute heart failure (AHF) developed delirium, and showed that preoperative cardiac function (including LVEF, BNP and NYHA functional classification) was independently related to POD[27]. Honda et al. demonstrated that 23% of AHF patients developed delirium during hospitalization and determined that there was an independent association between the NT-proBNP level and POD[28]. However, both studies were focused on patients specifically with AHF while our study showed similar results in all patients after cardiac surgery.

To the best of our knowledge, our study is the first prospective study to explore the association between preoperative cardiac function and POD based on a large sample of cardiac surgery patients. We found that both NYHA functional classification and NT-proBNP levels before surgery are related to delirium after cardiac surgery, meaning that they can be used as predictors of POD to guide clinical prevention. Both parameters are commonly used in clinical practice. The NT-proBNP level is more objective and accurate than the NYHA functional classification, while the NYHA functional classification is easier to acquire. In our study, the delirium assessors were blinded to the results of the NYHA functional classification assessment performed by the surgeons before surgery, thereby avoiding the assessment bias. In previous studies, the association between heart failure and cognitive impairment has been well described, but the relationship between heart failure and acute delirium has remained unclear. The prevalence of delirium is higher and has worse clinical outcomes in patients with heart failure than in other patient groups[27, 28]. Our study demonstrated the connection between preoperative cardiac function and the incidence of POD, which is consistent with the results of previous studies in nonsurgical patients. Closer monitoring and more intensive postoperative care in patients with an elevated preoperative NT-proBNP levels or higher NHYA classifications may further reduce the incidence of delirium after cardiac surgery.

According to the American Heart Association (AHA) statement on biomarkers for heart failure, a NT-proBNP level >450 pg/ml (=6.1 log transformed pg/ml) is considered significant for clinical diagnosis[29]. In our study, we found that a NT-proBNP turning point of 7.8 (log transformed pg/ml) could stratify the relationship between the preoperative NT-proBNP level and the risk of POD. The results showed that the OR of delirium increased with increasing NT-proBNP levels after the turning point of 7.8 (log transformed pg/ml). Our finding suggests that in clinical practice, we should pay more attention to patients who have preoperatively elevated NT-proBNP levels, especially those with levels higher than 7.8 (log transformed pg/ml). This can be a new predictor for the early detection of patients at high risk of developing POD and can help provide accurate risk stratification. Additionally, the early measures to improve cardiac function may reduce the risk of POD. Some studies have demonstrated that cerebral perfusion and cognitive dysfunction can be enhanced by improving cardiac function[30, 31].

The co-existence of heart failure and brain failure has been accepted for decades, first introduced in the 1970s with a description of cardiogenic dementia[10]. While the co-occurrence of heart failure and cognitive impairment is familiar to clinicians, this topic has received little attention compared with other characteristics of cardiac diseases[10]. Our study adds new evidence to the theory of the “heart-brain connection”. The brain depends on a continuous and adequate blood supply, and the interruption of cerebral blood flow leads to brain dysfunction and death[32]. There is abundant evidence showing that sufficient cerebral perfusion is a precondition for adequate cognitive functioning[33]. Cerebral perfusion is a function of cardiac output, arterial stiffness, the patency of cerebral arteries, cerebral autoregulation, the patency of small cerebral vessels, and venous patency. If any of these parameters changes, it can affect cognition. Thus, cardiac pathology affecting haemodynamics in the brain might influence its cellular functions before structures are irreversibly altered[34]. Therefore, the declining heart function might lead to acute cognitive impairment, we called delirium, through the affection between heart-brain connection.

Our study has several implications for clinical practice. The present findings indicate that delirium is a common and serious morbidity in patients after cardiac surgery. Since there is lack of effective treatments for delirium, prevention remains the best strategy. It is noteworthy that our study provides effective references for nurses to recognize high risk patients. Additionally, these cardiac parameters could be valuable predictors to develop prediction tools in future studies. Previous studies have proven that preventive measures could help reduce the incidence, duration and severity of delirium[35]. Therefore, patients with poor preoperative cardiac function, detailed preoperative education should be provided to patients including information about ICU environment and invasive treatment after surgery. Furthermore, for ICU nurses, pro-active monitoring delirium is important while attention should be paid regarding psychological care and early mobilization for these high risk patients[25]. These efforts to prevent the development of delirium may lead to be a better prognosis in patients after cardiac surgery.

Strengths and Limitations

Our study has several strengths compared to the previous studies. First, our study is the first prospective study to explore the predictors of POD based on a large sample of cardiac surgery patients in China. Our institute is the largest cardiac surgery centre in eastern China, admitted large amount and various types of cardiac surgery, which could be the representative of eastern China. Second, our study is a well-designed prospective research and the protocol was registered and published beforehand to provide transparency to the wider nursing research community. Finally, our study found the association between cardiac function and POD to substantiate the results of previous studies, also uncovered the non-linear relationship and the cut-off point by deeper exploration.

We acknowledge the potential limitations of our study. First, our participants were from a single institute in China, and the generalizability of the findings to other populations remains to be verified. Second, although the validated tools we used to detect delirium are highly sensitive and specific, patients with POD might be missed diagnosed because delirium status changes over time. However, we added extra assessments when patients had sudden changes in mental status or behaviours, which may have reduced the missed diagnosis rate. Thirdly, although alcohol use was reported as a risk factor of delirium in a previous study[36], no significant association was found in our study maybe due to the limited positive delirium patients. Finally, this study focused on the preoperative risk factors for delirium, and we did not fully consider the related factors after surgery in the Intensive Care Unit, which we aim to discuss in the follow-up study.

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CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

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Table 1. Baseline Characteristics of All Eligible Participants

Variable	Total	NYHA functional classification				P-value
		I	II	III	IV	
n (%)	635	53 (8.34%)	247 (38.90%)	318 (50.08%)	17 (2.68%)	
Age, y	57.42±12.69	51.02±13.46	54.66±13.11	60.68±11.20	56.35±13.89	<0.001
Male, n (%)	374 (58.90%)	31 (58.49%)	155 (62.75%)	173 (54.40%)	15 (88.24%)	0.017
Married*	462 (72.76%)	33 (91.67%)	178 (94.18%)	238 (93.70%)	13 (86.67%)	0.678
Nicotine use, n (%)	232 (36.54%)	21 (39.62%)	89 (36.03%)	112 (35.22%)	10 (58.82%)	0.248
Alcohol use, n (%)	208 (32.76%)	21 (39.62%)	86 (35.10%)	91 (28.71%)	10 (58.82%)	0.025
Hypertension, n (%)	234 (36.85%)	17 (32.08%)	93 (37.65%)	119 (37.42%)	5 (29.41%)	0.792
Diabetes mellitus, n (%)	57 (8.98%)	4 (7.55%)	22 (8.91%)	30 (9.43%)	1 (5.88%)	0.937
Peripheral vascular disease, n (%)	14 (2.20%)	3 (5.66%)	6 (2.43%)	4 (1.26%)	1 (5.88%)	0.146
Cerebrovascular disease, n (%)	16 (2.52%)	1 (1.89%)	7 (2.83%)	8 (2.52%)	0 (0.00%)	0.891
History of surgery	298 (46.93%)	18 (33.96%)	121 (49.19%)	151 (47.63%)	8 (47.06%)	0.247
History of cardiac surgery, n (%)	14 (2.20%)	0 (0.00%)	4 (1.62%)	8 (2.52%)	2 (11.76%)	0.030
Visual impairment, n (%)	361 (56.85%)	20 (37.74%)	115 (46.56%)	219 (68.87%)	7 (41.18%)	<0.001
Hearing impairment, n (%)	63 (9.92%)	2 (3.77%)	21 (8.50%)	40 (12.58%)	0 (0.00%)	0.066
Preoperative Anxiety, n (%)	21 (3.31%)	2 (3.77%)	4 (1.62%)	14 (4.40%)	1 (5.88%)	0.286
Preoperative Depression, n (%)	18 (2.83%)	0 (0.00%)	6 (2.43%)	10 (3.14%)	2 (11.76%)	0.081
ADL<80, n (%)	38 (5.98%)	4 (7.55%)	9 (3.64%)	21 (6.60%)	4 (23.53%)	0.007
Pain score, 0-10	0.15±0.55	0.17 ± 0.55	0.15 ± 0.58	0.15 ± 0.54	0.06 ± 0.24	0.910
Preoperative sleeping quality, n (%)						0.008
Good	181 (28.50%)	23 (43.40%)	74 (29.96%)	81 (25.47%)	3 (17.65%)	
Moderate	324 (51.02%)	26 (49.06%)	130 (52.63%)	161 (50.63%)	7 (41.18%)	
Poor	130 (20.47%)	4 (7.55%)	43 (17.41%)	76 (23.90%)	7 (41.18%)	
LVEF, %	62.33±7.64	64.60±6.67	63.51±5.84	61.60±8.07	51.88±13.83	<0.001
NT-proBNP, log transformed pg/ml	5.71±1.58	4.91±1.76	5.33±1.52	6.05±1.46	7.61±0.74	<0.001
BUN, mmol/l	6.44±2.17	5.61 ± 1.45	6.28 ± 2.01	6.54 ± 2.20	9.50 ± 3.12	<0.001
Duration of surgery, min	266.84±96.19	269.11 ± 111.45	257.98 ± 93.16	272.53 ± 95.51	282.00 ± 100.11	0.300
Duration of CPB, min	98.59±49.96	95.23 ± 47.61	91.81 ± 48.19	102.92 ± 50.57	126.71 ± 56.65	0.005
Duration of aortic cross clamp, min	57.23±38.54	58.72 ± 45.85	52.73 ± 35.06	58.92 ± 39.47	69.47 ± 40.63	0.086
Intraoperative blood transfusion, n (%)	103 (16.22%)	6 (11.32%)	35 (14.17%)	57 (17.92%)	5 (29.41%)	0.207

Present of postoperative delirium, n (%)	73 (11.50%)	5 (9.43%)	14 (5.67%)	47 (14.78%)	7 (41.18%)	<0.001

Data presented as mean±SD for continuous variables and percentage for discontinuous variables. NYHA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal prohormone of Brain Natriuretic Peptide; ADL, Activities of Daily Living; BUN, Blood Urea Nitrogen; CPB, Cardiopulmonary Bypass; *, Other patients including unmarried, divorced and widowed.

Table 2. Multivariate Regression for Effect of Preoperative NT-proBNP, NYHA functional classification, and LVEF on the Postoperative Delirium

Variable	Incidence, n (%)	Crude Model OR (95% CI)	Crude Model P Value	Crude Model P for Trend	Multivariate-Adjusted Model 1 OR (95% CI)	Model 1 P Value	Model 1 P for Trend	Multivariate-Adjusted Model 2 OR (95% CI)	Model 2 P Value	Model 2 P for Trend
NT-proBNP										
NT-proBNP (continuous), log transformed pg/ml		1.47 (1.24, 1.74)	<0.001		1.32 (1.09, 1.60)	0.004		1.24 (1.01, 1.52)	0.044	
Tertiles										
T1:	13 (6.13%)	1.0		<0.001	1.0		0.040	1.0		0.223
T2:	23 (11.00%)	1.89 (0.93, 3.85)	0.078		1.46 (0.68, 3.13)	0.344		1.37 (0.62, 3.01)	0.431	
T3:	37 (17.29%)	3.20 (1.65, 6.21)	<0.001		2.07 (1.01, 4.27)	0.048		1.63 (0.75, 3.55)	0.219	
NYHA functional classification										
Ⅰ	5 (9.43%)	1.0		<0.00	1.0		0.002	1.0		0.008
Ⅱ	14 (5.67%)	0.58 (0.20, 1.68)	0.312	1	0.49 (0.16, 1.55)	0.224		0.46 (0.14, 1.50)	0.198	
Ⅲ	47 (14.78%)	1.66 (0.63, 4.40)	0.304		1.21 (0.42, 3.51)	0.720		1.13 (0.38, 3.29)	0.830	
Ⅳ	7 (41.18%)	6.72 (1.77, 25.53)	0.005		6.23 (1.45, 26.66)	0.014		3.90 (0.83, 18.28)	0.084	
Binary										
Ⅰ + Ⅱ	19 (6.33%)	1.0		-	1.0		-	1.0		-
Ⅲ + Ⅳ	54 (16.12%)	2.84 (1.64, 4.92)	<0.001		2.46 (1.35, 4.49)	0.003		2.34 (1.27, 4.31)	0.007	
LVEF										
LVEF (continuous), %		0.97 (0.94, 1.00)	0.029		0.97 (0.94, 1.01)	0.099		0.98 (0.95, 1.01)	0.223	
Tertiles										
T1:	25 (11.79%)	1.0		0.220	1.0		0.619	1.0		0.870
T2:	28 (15.38%)	1.36 (0.76, 2.43)	0.299		1.36 (0.73, 2.54)	0.327		1.48 (0.78, 2.83)	0.175	
T3:	20 (8.30%)	0.68 (0.36, 1.26)	0.217		0.83 (0.43, 1.62)	0.590		0.93 (0.47, 1.85)	0.837	

NT-proBNP, NYHA functional classification, LVEF were first individually entered into model 1 and then simultaneously entered into model 2. Model 1 adjusted for age, sex, cerebrovascular disease, duration of surgery, intraoperative blood transfusion; Model 2 adjusted for age, sex, cerebrovascular disease, duration of surgery, intraoperative blood transfusion, peripheral vascular disease, hypertension, diabetes mellitus, hyperlipidemia, preoperative anxiety, depression, ADL, BUN. CI indicates Confidence Interval; OR, Odds Ratio; NT-proBNP, N-Terminal prohormone of Brain Natriuretic Peptide; NHYA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; BUN, Blood Urea Nitrogen.

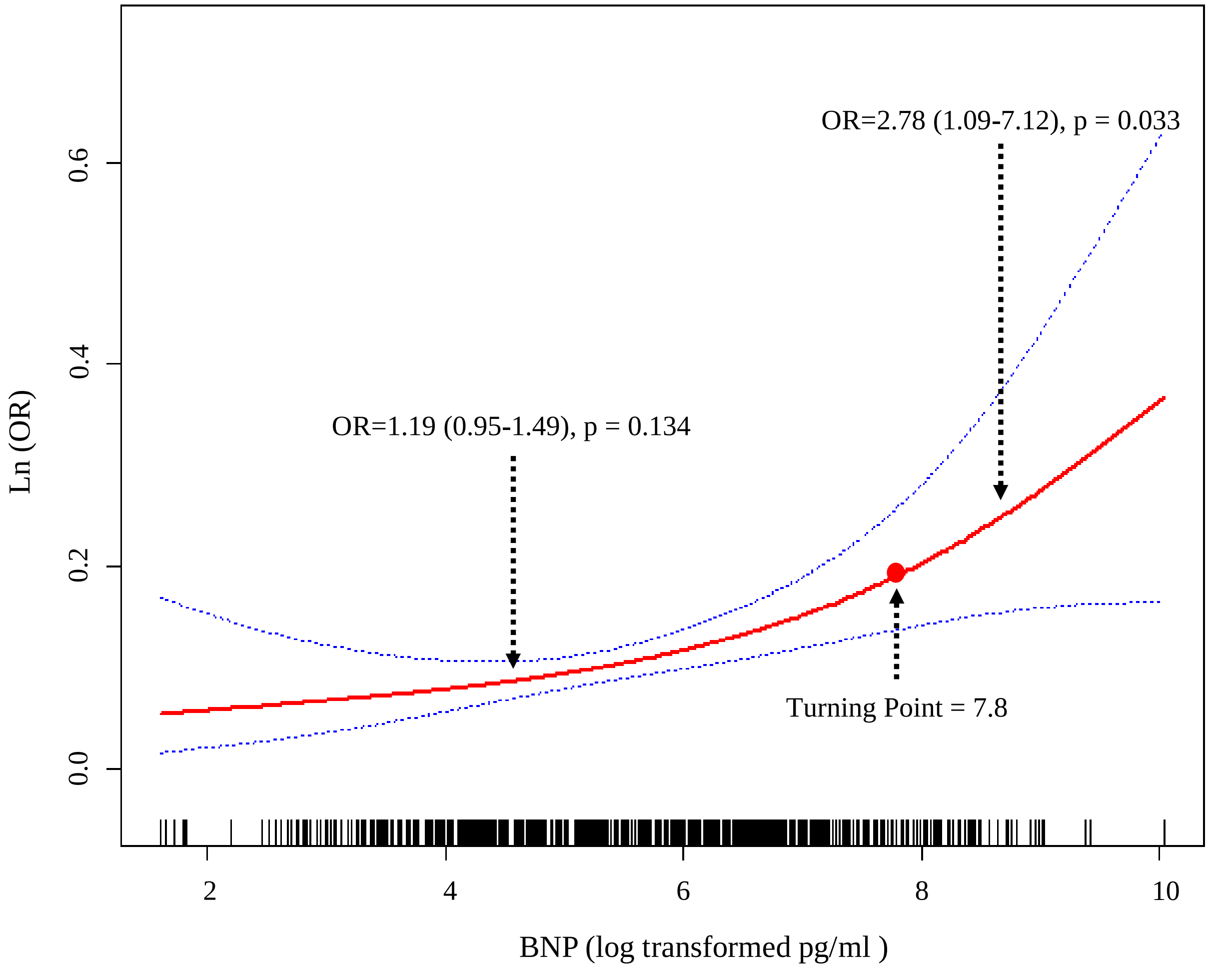

Figure 1. Non-linear relationship between log NT-proBNP and log odd ratio of delirium after controlling for potential confounding variables (Multivariate odd ratios, 95% confidence intervals and p value are shown)

Subgroup	No. of Patients (%)	Odds Ratio (95%CI)	P−value for Interaction
Overall	635 (100)	2.84 (1.64–4.92)	
Age			0.726
<60	310 (49)	2.89 (1.2–6.97)	
>=60	325 (51)	2.36 (1.16–4.81)	
Gender			0.802
Male	374 (59)	2.73 (1.38–5.39)	
Female	261 (41)	3.17 (1.24–8.1)	
Nicotine use			0.845
No	403 (63)	2.72 (1.29–5.77)	
Yes	232 (37)	3.04 (1.36–6.82)	
Alcohol use			0.081
No	424 (67)	2.01 (1.04–3.89)	
Yes	117 (18)	14 (1.76–111.63)	
Hypertension			0.805
No	401 (63)	5.02 (2.17–11.62)	
Yes	234 (37)	1.57 (0.73–3.38)	
Diabetes mellitus			0.045
No	578 (91)	2.91 (1.63–5.18)	
Yes	57 (9)	2.31 (0.41–13.03)	
History of surgery			0.363
No	335 (53)	3.81 (1.61–9.05)	
Yes	298 (47)	2.26 (1.1–4.64)	
Preoperative Depression			0.678
<11	617 (97)	2.88 (1.64–5.05)	
>=11	18 (3)	1.67 (0.14–20.58)	
ADL			0.106
<80	38 (6)	0.88 (0.2–3.79)	
>=80	597 (94)	3.24 (1.77–5.94)	
Preoperative sleeping quality			0.709
Good	181 (29)	3.68 (1.27–10.7)	
Moderate	324 (51)	2.98 (1.44–6.17)	
Poor	130 (20)	1.78 (0.46–6.94)	
Intraoperative blood transfusion			0.318
No	532 (84)	3.32 (1.65–6.68)	
Yes	103 (16)	1.82 (0.71–4.68)	

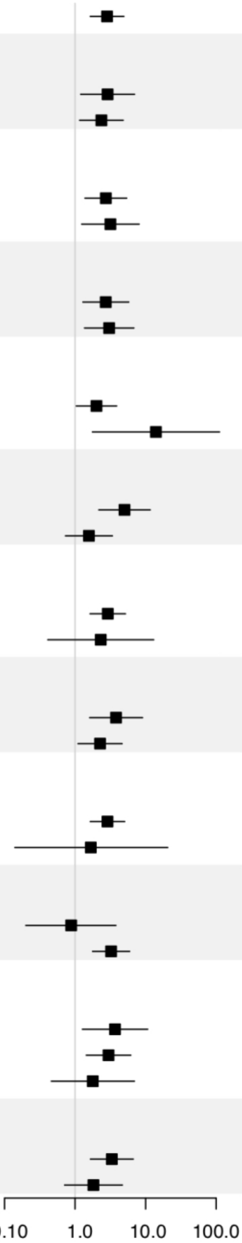

Figure 2. Subgroup analysis for effect of NYHA functional classification on the risk of incident delirium after cardiac surgery

Table S1. Baseline Characteristics of Participants According to Delirium Outcome Available or not

Variable	Total (n=708)	Delirium Outcome Available		
		Yes (n=635)	No (n=73)	P-value
Age, y	57.38±12.81	57.42±12.69	57.08±13.97	0.835
Male, n (%)	419 (59.26%)	374 (58.90%)	45 (62.50%)	0.555
Married*	518 (73.16%)	462 (72.76%)	56 (76.71%)	0.470
Nicotine use, n (%)	348 (49.15%)	232 (36.54%)	25 (34.25%)	0.057
Alcohol use, n (%)	230 (36.22%)	208 (32.76%)	22 (30.14%)	0.651
Hypertension, n (%)	262 (37.06%)	234 (36.85%)	28 (38.89%)	0.734
Diabetes mellitus, n (%)	64 (9.05%)	57 (8.98%)	7 (9.72%)	0.834
Peripheral vascular disease, n (%)	15 (2.12%)	14 (2.20%)	1 (1.39%)	0.649
Cerebrovascular disease, n (%)	16 (2.26%)	16 (2.52%)	0 (0.00%)	0.173
History of surgery	333 (47.10%)	298 (47.08%)	35 (48.61%)	0.786
History of cardiac surgery, n (%)	17 (2.40%)	14 (2.20%)	3 (4.17%)	0.303
Visual impairment, n (%)	401 (56.72%)	361 (56.85%)	40 (55.56%)	0.834
Hearing impairment, n (%)	70 (9.90%)	63 (9.92%)	7 (9.72%)	0.957
Preoperative Anxiety, n (%)	21 (2.97%)	21 (3.31%)	0 (0.00%)	0.225
Preoperative Depression, n (%)	21 (2.97%)	18 (2.83%)	3 (4.11%)	0.543
ADL<80, n (%)	43 (6.07%)	38 (5.98%)	5 (6.85%)	0.769
Pain score, 0-10	0.15±0.55	0.15±0.55	0.15±0.52	0.981
Preoperative sleeping quality, n (%)				0.289
Good	196 (27.72%)	181 (28.50%)	15 (20.83%)	
Moderate	362 (51.20%)	324 (51.02%)	38 (52.78%)	
Poor	149 (21.07%)	130 (20.47%)	19 (26.39%)	
LVEF, %	62.13±7.96	62.33±7.64	60.33±10.20	0.043
NT-proBNP, log transformed pg/ml	5.72±1.58	5.71±1.58	5.72±1.59	0.992
Hemoglobin, (g/l)	133.01±19.17	132.94±19.12	133.61 ± 19.69	0.779
CRE, umol/l	84.67±24.05	84.03±22.70	90.31 ± 33.42	0.036
BUN, mmol/l	6.48±2.25	6.44±2.17	6.84± 2.79	0.152
Duration of surgery, per 30 min	8.88±3.20	8.89±3.21	8.79 ± 3.19	0.796
Duration of CPB, per 30 min	3.31±1.72	3.29±1.67	3.58 ± 2.12	0.164

Duration of aortic cross clamp, per 30 min	1.89±1.28	1.91±1.28	1.78 ± 1.24	0.411
Intraoperative blood transfusion, n (%)	114 (16.10%)	103 (16.22%)	11 (15.07%)	0.800
NYHA functional classification, n (%)				0.928
I	59 (8.33%)	53 (8.34%)	6 (8.22%)	
II	276 (38.98%)	247 (38.90%)	29 (39.73%)	
III	355 (50.14%)	318 (50.08%)	37 (50.68%)	
IV	18 (2.54%)	17 (2.68%)	1 (1.37%)	

Data presented as mean±SD for continuous variables and percentage for discontinuous variables. NHYA, New York Heart Association; LVEF, Left Ventricular Ejection Fraction; NT-proBNP, N-Terminal prohormone of Brain Natriuretic Peptide; CRE, Serum creatinine; ADL, Activities of Daily Living; BUN, Blood Urea Nitrogen; CPB, Cardiopulmonary Bypass; *, Other patients including unmarried, divorced and widowed.

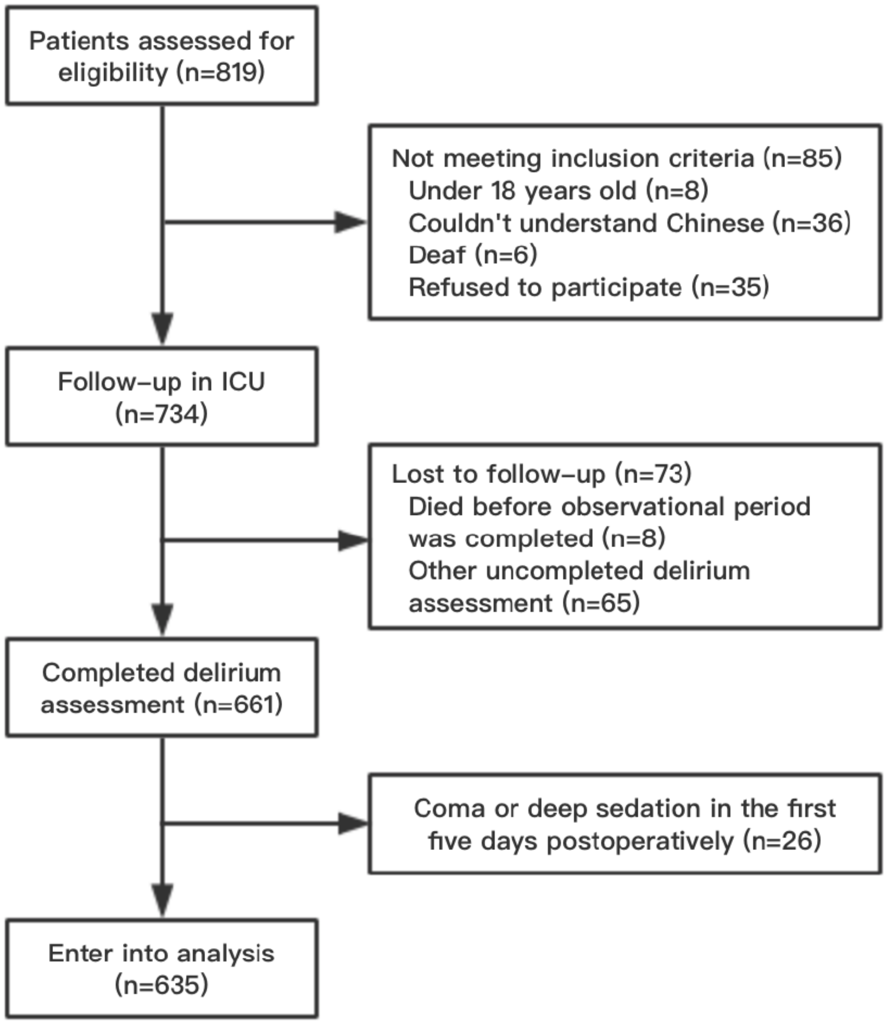

Figure S1. Flow chart of patients recruitment